REMARKS

Status of the Claims

Claims 10 and 22-29 are pending, and are as previously presented. No new matter has been added.

Claim Rejection under 35 U.S.C. § 103(a)

Claims 10 and 22-29 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gensthaler (Pharmazeutische Zeitung, 2001, 146(7): 35-36) ("Gensthaler") in view of Leynadier *et al.* (Acta Ortorhinolaryngol Bel, 2001, 55(4): 305-312) ("Leynadier"), and over Salmun *et al.* (US2003/0236275) ("Salmun"). The applicants respectfully traverse.

The obviousness analysis we recently addressed by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727; 167 L. Ed. 2d 705; 2007 U.S. LEXIS 4745; 82 U.S.P.Q.2D (BNA) 1385 (April 30, 2007) and the PTO's subsequent examination guidelines at 72 Fed. Reg. 57,526 (2007).

As recognized in the PTO guidelines, the Court considered predictability an important factor in the obvious analysis:

> The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.

Id. at 1739 (*emphasis added*). The Court also stated:

> When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, *§ 103* likely bars its patentability.

Id. at 1740 (*emphasis added*).

> [I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* and *Anderson's-Black Rock* are illustrative -- a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

Id. (*emphasis added*). As explained below, no such predictability in achieving the results of the presently claimed invention was possible at the priority date.

Other factors the Court reiterated as important in the obviousness analysis are teachings away from the claimed invention and the prohibition against hindsight reconstruction of it.

"When the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *Id.* at 1740 (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)). And, while cautioning against "[r]igid preventive rules that deny fact-finders recourse to common sense," the Court nevertheless reiterated its holding in *Graham*, cautioning the fact-finder against falling prey to "the distortion caused by hindsight bias" and "*ex post reasoning*." *KSR*, 127 S. Ct. at 1742 (citing *Graham*, 383 U.S., at 36, "'warning against a "temptation to read into the prior art the teachings of the invention in issue' and instructing courts to 'guard against slipping into the use of hindsight.'").

With the foregoing legal framework in mind, first and foremost, it is important to recognize that persistent allergic rhinitis (PER) is a separate and distinct disease from both seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR):

(1) Historical subdivision of allergic rhinitis into seasonal, perennial and occupational rhinitis

Historically, allergic rhinitis was subdivided according to the time of allergen exposure into seasonal, perennial and occupational rhinitis [Intl Consensus Report, *Allergy*, 1994; Dykewicz, et al. *J Allergy Clin Immunol*, 2003; Dykewicz, et al. *Ann Allergy Asthma Immunol*, 1998; van Cauwenberge, et al. *Allergy*, 2000]. Seasonal allergic rhinitis (SAR) was related to a wide variety of outdoor allergens such as pollens or molds. Perennial allergic rhinitis (PAR) was thought to be most frequently caused by indoor allergens such as dust mites, molds, insects and animal dander. Occupational allergic rhinitis referred to rhinitis arising in response to substances in the workplace, which may be mediated by allergic or nonallergic factors, e.g. laboratory animals, grain, wood, dust, latex and chemicals.

This previous classification, however, is not adherent to real life as it is difficult to clearly define the pollen season in most patients [Walls, et al. *Med J Aust*, 2005]. In certain areas, pollens and molds are perennial allergens [Bucholtz, et al. *Ann Allergy*, 1991; D'Amato, et al. *J Allergy Clin Immunol*, 1989]. Also, the majority of patients are sensitized to many different allergens and, therefore, show symptoms throughout the year [Sibbald, et al. *Thorax*, 1991; *see also* Bosquet, et al. *Clin Exp Allergy*, 2005; Bauchau, et al. *Eur Respir J*, 2004; Arbes, et al. *J Allergy Clin Immunol*, 2005;; Ciprandi, et al. *Allergy*, 2005]. Further, due to the priming effect on the nasal mucosa induced by low levels of pollen allergens [Connell JT, *J Allergy*, 1969; Wachs, et al. *J Allergy Clin Immunol*, 1989; Juliusson, et al. *Clin Allergy*, 1988] and minimal

persistent inflammation of the nose in patients with symptom-free rhinitis [Knani, et al. *J Allergy Clin Immunol*, 1992; Cipransi, et al. *J Allergy Clin Immunol*, 1995; Ricca, et al. *J Allergy Clin Immunol*, 1999], symptoms do not necessarily occur strictly in conjunction with the allergen exposure. Furthermore, symptoms of perennial allergy may not always be present all year round and most patients with perennial allergen sensitization have intermittent rhinitis [Cipransi, et al. *J Allergy Clin Immunol*, 1995; *see also* Bauchau, et al. *Eur Respir J*, 2004; Bauchau, et al. *Allergy*, 2005].

(2) Reclassification of allergic rhinitis as intermittent allergic rhinitis (IAR) and persistent allergic rhinitis (PER).

For the foregoing reasons, it was recognized that the categories of seasonal, perennial and occupational allergic rhinitis did not describe allergic rhinitis sufferers sharing a single or closely related set of etiologies. Even the classic types of seasonal and perennial rhinitis (descriptions of conditions now disfavored, see below) cannot be used interchangeably, as they do not represent the same stratum of disease.[Bousquet, et al. *J Allergy Clin Immunol*, 2001; see also Bousquet, et al. *Clin Exp Allergy*, 2005; Bauchau, et al. *Eur Respir J*, 2004; Demoly, et al. *Allergy*, 2003].

Following an extensive review of the literature available prior to December 1999, an international panel of experts at the Allergic Rhinitis and its Impact on Asthma World Health Organization workshop (ARIA) recognized distinctions among a variety of conditions previously collectively termed "allergic rhinitis" and issued an evidence-based document establishing a new classification system [Bousquet, et al. *J Allergy Clin Immunol*, 2001]. The most important aspect of ARIA was the subdivision of allergic rhinitis into "intermittent" (IAR) and "persistent" disease (PER). The ARIA classification was found to be of value in several large independent studies carried out in different countries.

As a result of this reclassification, patients who would have been previously diagnosed with SAR represented a different group than those who would be diagnosed with PER.

(3) Subclassification of allergic rhinitis based on severity of symptoms and quality of life

A second important issue of the ARIA guidelines was the classification of severity, which was categorized as "mild" and "moderate-severe". It is now recognized that allergic rhinitis comprises more than the classical symptoms of sneezing, rhinorrhea and nasal obstruction — allergic rhinitis is associated with impairments in how patients function in day-to-day life

[Leynaert, et al. *Am J Respir Crit Care Med*, 2000; Bousquet, et al. *J Allergy Clin Immunol*, 1994; Juniper, et al. *J Allergy Clin Immunol*, 1994; Roberts, et al. *J Allergy Clin Immunol*, 2003]. Allergic rhinitis is also associated with sleeping difficulties for some patients [McNicholas, et al. *Am Rev Respir Dis*, 1982].

Even though some think that the severity of rhinitis may be classified as mild, moderate and severe, the classification of IAR and PER has not been disputed at all. ARIA proposed also a stepwise management taking into account both persistence and severity, suggesting different management of mild IAR, mild PER and moderate-severe IAR and moderate-severe PER [Bousquet, et al. *J Allergy Clin Immunol*, 2001]. The ARIA new update (in press) maintains the same stepwise approach.

Gensthaler in view of Leynadier *et al.*

The Office rejects claims as being obvious over Gensthaler in view of Leynadier *et al.*, and alleges that "it would have been obvious to one of ordinary skill in the art to administer levocetirizine in the treatment of PER because Gensthaler teaches the effectiveness of the compound in SAR and further teaches the intended clinical study of PER with the same compound". But as explained above, at the time of the present invention, one skilled in the art would not have considered the results observed in treatment of SAR as predictive of the results that would be achieved treating PER.

Furthermore, as clearly stated in the ARIA document, studies should be undertaken in PER since there was no evidence that medications, including levocetirizine, would have a similar therapeutic effect. Therefore the results achieved with levocetirizine or any other medications up to 1999 were not sufficiently predictable for one of ordinary skill in the art to conclude that it would have a similar effect in both SAR and PER [Bousquet, et al. *J Allergy Clin Immunol*, 2001].

Thus, Gensthaler's teachings of treatment of SAR do not render the claims obvious because, at the time of filing, SAR was recognized as not being descriptive of a single, well characterized condition. Accordingly, the results of treating with levocetirizine patients previously characterized as suffering from SAR were not considered to be sufficiently predictive of the results of using levocetirizine to treat patients suffering from PER. Indeed, separate

clinical trials were warranted. Following *KSR v. Teleflex*, 127 S.Ct. 1727 (2007), the lack of predictability makes the present claims non-obvious.

Furthermore, Gensthaler's teaching of intended clinical study of PER with levocetirizine does not render the claims obvious because Gensthaler does not provide an enabling disclosure. Gensthaler merely informs of an intent to conduct a study on the use of levocetrizine for the treatment of patients with PER. No other details of the study are provided (e.g. dosage, administration regime, duration of treatment, administration route, etc.), just a statement that the study director "hopes that the study ... and their treatment will portray a comprehensive view of allergic patients and their treatment over the course of the year." Rather, the Office relies on Leynadier for its teaching of 2.5, 5 and 10 mg/day dosages of levocetirizine for the treatment of SAR. Like Gensthaler, Leynadier neither teaches nor suggests anything regarding using levocetirizine for the treatment of PER, as presently claimed. One of ordinary skill in the art could not have predicted that the dosages taught by Leynadier, or any other possible dosage for that matter, would have been effective for treating PER. In addition, neither Gensthaler nor Leynadier teach the duration of treatment required to achieve and maintain an effect in PER. Therefore, Leynadier fails to compensate for the deficiencies of Gensthaler.

The Office further alleges that "one of ordinary skill in the art would have been motivated to administer levocetirizine in the treatment of PER". However, prior to the filing date of this patent application no antihistamine had been studied for the treatment of PER. While it may have been surmised that antihistamines are "generally" effective in alleviating at least some of the symptoms of allergic rhinitis in general, this did not allow anyone to conclude that levocetirizine, in particular, would be significantly effective in a very specific subgroup (PER patients). In fact, physicians believed that the continuous therapeutic effect would be lost over time due to the relatively important placebo effect [Meltzer, et al. *Clin Drug Invest*, 2001; Berger, et al. *Ann Allergy Ashtma Immunol*, 2002; Simons et al. *J Allergy Clin Immunol*, 2003]. (The placebo effect is generally very high in allergic rhinitis, so the long term efficacy (six months) is a real challenge). Consequently, it was unknown whether levocetirizine would be superior to placebo for treatment of PER. That is, it was not "obvious" that levocetirizine (or any other antihistamine) could demonstrate clinical efficacy in this new indication.

The Xpert® study [Bachert et al. *J Allergy Clin Immunol*, 2004] was a pioneering trial performed with levocetirizine after the priority date of the present application. Even at the time

of its inception, the Xpert® study was characterized as extremely risky because there was great uncertainty of the long term effect (over six months) of levocetirizine on a more severe population; FDA guidelines at the time provided that such studies should be conducted over only a 2 or 4 week period. It was only *after* the results of the Xpert® study on classical acute rhinitis symptoms and on long term maintenance of these symptoms were surprisingly positive that the ARIA update approved levocetirizine for the treatment of PER. Because of the uncertainties prior to the trial (and prior to the present invention), the results achieved were not predictable.

Thus, prior to the filing date, there was no indication that PER could be treated with antihistamines in general or levocetirizine in particular, and those of ordinary skill in the art were taught away from long term continuous therapy. That being the case, the present claims cannot be obvious over Gensthaler in view of Leynadier. Accordingly, reconsideration and withdrawal of this obviousness rejection is respectfully requested.

Salmun *et al.*

Salmun *et al.* teaches use of desloratadine and/or other antihistamines for treating SAR. As a result, the Office rejected claims as being obvious over Salmun *et al.*, and alleged that "it would have been obvious to one of ordinary skill in the art at the time of the invention to administer levocetirizine in the treatment of persistent allergic rhinitis because of the teachings of Salmun" and that "it would have been obvious to one of ordinary skill in the art at the time of the invention to administer an antihistamine such as desloratadine or levocetirizine in the treatment of persistent allergic rhinitis, as Salmun teaches that the antihistamine compound provides significant relief of persistent allergic rhinitis symptoms such as congestion/stuffiness". First, as explained above the results achieved in treating "seasonal allergic rhinitis" with levocetirizine were not considered predictive of the results of treating persistent allergic rhinitis (PER) with levocetirizine.

Second, Applicants respectfully submit that Salmun never mentions PER in the definition of allergic and inflammatory conditions (see Salmun paragraph [0012]). The Office points to paragraph [0050], which states: "significant relief from persistent allergic symptoms such as nasal congestion/stuffiness **in patients with SAR**." (Emphasis added.) Thus, Salmun is not referring to *PER* but to persistent symptoms of *SAR*. That is, persistent allergic symptoms in SAR should not be confused with persistent allergic rhinitis (PER) disease.